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Urinary electrolyte monitoring in critically ill patients: a preliminary observational study

Monitorização de eletrólitos urinários em pacientes críticos: estudo preliminar observacional

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ABSTRACT

Objective: Intensive care unit survivors and non-survivors have distinct acid-base profiles. The kidney's regulation of urinary electrolytes and the urinary strong ion difference plays a major role in acid-base homeostasis. The aim of this study was to evaluate the potential utility of daily spot urinary electrolyte measurement in acid-base and renal function monitoring.

Methods: We prospectively recorded daily plasma acid-base parameters and traditional markers of renal function in parallel with spot urinary electrolyte measurements in patients with urinary catheters admitted to our intensive care unit. Patients who remained in the intensive care unit for at least 4 days with a urinary catheter were included in the study.

Results: Of the 50 patients included in the study, 22% died during their intensive care unit stay. The incidence of acute kidney injury was significantly higher in non-survivors during the 4-day observation period (64% vs. 18% in survivors). Urinary chloride and sodium were lower and urinary strong ion difference was higher on day 1 in patients who developed acute kidney injury among both survivors and non-survivors. Both groups had similar urine output, although non-survivors had persistently higher urinary strong ion difference on all days. Survivors had a progressive improvement in metabolic acid-base profile due to increases in the plasma strong ion difference and decreases in weak acids. These changes were concomitant with decreases in urinary strong ion difference. In non-survivors, acid-base parameters did not significantly change during follow-up.

Conclusions: Daily assessment of spot urinary electrolytes and strong ion difference are useful components of acid-base and renal function evaluations in critically ill patients, having distinct profiles between intensive care unit survivors and non-survivors.

Keywords: Critical care; Acidosis; Water-electrolyte imbalance; Acute kidney injury; Monitoring, physiologic; Prognosis

INTRODUCTION

Managing acid-base disturbances in critically ill patients is an important part of treatment. The physicochemical approach proposed by Stewart[1] and modified by Figge[2] has recently gained recognition as a useful tool for the interpretation of complex acid-base imbalances. In this approach, two variables in addition to $PaCO_2$ are considered determinants of H^+ concentration and, hence, pH. These two variables are the strong ion difference (SID) and the

total amount of non-volatile weak acids. SID is the difference between completely dissociated cations (Na^+, K^+, Ca^{2+}, Mg^{2+}) and anions (Cl^-, lactate$^-$) normally present in physiological solutions. Under normal conditions, the total amount of non-volatile weak acids is the sum of albumin and phosphate, both of which are only partially dissociated at a pH compatible with human life.

Extracellular SID variation appears to be the major determinant of the metabolic acid-base state in critically ill patients.[3] Decreases in SID induce water dissociation and increase concentrations of free protons (hence decreasing pH) to maintain electroneutrality. Increases in SID induce increases in pH for the opposite reason. The kidneys play a major role in acid-base homeostasis. From a physicochemical point of view, this is due in great part to changes in urinary SID (SIDu). In normal physiology, both plasma and urinary SID values are the same (approximately 42 mEq/L),[3] and in urine, SID = $[Na^+] + [K^+] - [Cl^-]$. Under normal conditions, the kidneys respond to decreases in plasma SID by increasing ammonium (NH_4^+) excretion, the main mechanism of increasing urinary acid load.[4-6] To counterbalance NH_4^+ excretion and maintain electroneutrality, urinary excretion of Cl^- increases in relation to Na^+ and K^+, decreasing the SIDu.

Although there are still many concerns about the SID approach,[7] especially in a mechanistic sense, it has gained popularity in critical care settings in recent years.[8] However, its use has been generally restricted to plasma SID, and few studies have focused on SIDu and the relevant information it may provide.[9-11] Urinary electrolyte measurements are usually utilized in the intensive care unit (ICU) for the differential diagnosis of natremia disorders, the diagnosis of pre-renal versus acute tubular necrosis, and determining the etiology of hyperchloremic metabolic acidosis. However, these urinary markers still need to be adequately studied and validated in the critical care setting. Critically ill patients frequently receive large volumes of low SID solutions (e.g., normal saline) in addition to endogenous production of sulfates, phosphates, lactate, and ketoacids, as well as other components that increase the acid load and decrease plasma SID. Using a Stewart acid-base approach, normal kidneys are expected to produce urine with a low SIDu to maintain a stable plasma SID. In contrast, injured kidneys are expected to not respond with adequate ammonium excretion but instead produce urine with a higher SID, contributing to the generation of metabolic acidosis.

In a previous study,[12] we showed that ICU survivors showed progressive adjustment in their metabolic acid-base profile, in contrast to ICU non-survivors. The aim of the present study was to evaluate daily urinary electrolytes and SIDu in ICU survivors and non-survivors, in parallel with other parameters routinely assessed, to evaluate acid-base status and kidney function. In this preliminary study, our aim was to describe possible differences between ICU survivors and non-survivors in urinary biochemistry in the first 4 ICU days. Our hypothesis is that urinary electrolyte monitoring would be helpful in distinguishing patients that will develop AKI in the first 4 ICU days and have a poor ICU outcome.

METHODS

The Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo Ethics Committee approved the study (protocol number 0093/11), and the need for informed, written consent was waived by the same committee. The study was conducted prospectively in a single medical 6-bed ICU, which occasionally receives surgical and trauma patients. Blood used in this study was collected routinely once daily, between 8 p.m. and 10 p.m., from every patient in our ICU. The laboratory analyses included arterial blood gases, arterial lactate, blood urea nitrogen (BUN), creatinine, Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, phosphate and albumin. In addition, starting from October 2009, we included a spot urine sample as part of the routine exams. However, this sample was only taken from patients with a urinary catheter in place when blood was being collected. In this spot urine sample, Na^+ (NaU), K^+ (KU), Cl^- (ClU) and creatinine (CrU) were measured, and the 2-h creatinine clearance was calculated using the 8 p.m. to 10 p.m. urine volume (the collection bag is emptied every 2 hours in our ICU). In addition, the SIDu, standard base excess (SBE), apparent strong ion difference (SIDa), effective strong ion difference (SIDe), strong ion gap (SIG) and fractional excretion of sodium (FENa) were calculated daily using the laboratory values previously mentioned (see formulas below). For the purposes of this study, we analyzed only the patients who had a urinary catheter inserted before or at the time of ICU admission and had that catheter for the first 4 days of their ICU stay. We excluded patients who were discharged, died, needed renal replacement therapy, or had the urinary catheter removed during the first 4 days in the ICU. Patients with massive hematuria, urinary irrigation, neobladder, kidney transplant, or chronic renal failure and patients

who were readmitted to the ICU or transferred to another ICU were also excluded. Urinary catheter insertion and removal was at the discretion of the assistant physician and not influenced by the ongoing study.

Patient demographics, associated comorbidities, severity scores (Simplified Acute Physiology Score *3* - SAPS 3[13] and Sequential Organ Failure Assessment - SOFA[14]), 24-h urine output, fluid balance, use of vasopressors, bicarbonate, diuretics, the need for mechanical ventilation during the 4-day study period and dialysis after the 4 days of observation were all recorded.

Acute kidney injury diagnosis

Acute kidney injury (AKI) was defined using AKIN[15] criteria (creatinine only) during the 4-day observation period. The lowest creatinine in the previous 48 hours before admission was considered the baseline renal function. For patients without a creatinine measurement in the previous 48 hours, the value on admission was considered the baseline renal function. For the purposes of this study, patients were classified as having AKI if they met any stage of AKIN creatinine criteria during the 4 days of observation.

Laboratory techniques and measurements

All samples were analyzed in the central laboratory of the institution. Serum Na^+, K^+, Ca^{2+} and Cl^- concentrations were measured using the direct ion-selective electrode technique. Mg^{2+} was measured using a colorimetric technique, and phosphate was measured using an ultraviolet technique. BUN was measured with a kinetic technique, and albumin was measured with a bromocresol dye colorimetric technique. NaU, KU, and ClU were also measured using the direct ion-selective electrode technique, while creatinine was measured in both serum and urine using a kinetic colorimetric technique. Arterial blood gases were analyzed, and lactate was measured on the OMNI analyzer (Roche Diagnostics System, F. Hoffmann-La Roche Ltd., Basel, Switzerland). Values for SBE, SIDa, SIDe, SIG and FENa were calculated using standard formulas: SBE (Van Slyke equation) (mEq/L) = $0.9287 \times (HCO_3^-$ (mmol/L) - 24.4 + 14.83 × [pH - 7.4]); SIDa (mEq/L) = Na^+ (mEq/L) + K^+ (mEq/L) + Ca^{2+} (mEq/L) + Mg^{2+} (mEq/L) - [Cl^- (mEq/L) + lactate$^-$ (mEq/L)]; SIDe (mEq/L) = $2.46 \times 10^{-8} \times PCO_2/10^{-pH}$ + [albumin (g/L) × (0.123 × pH – 0.631)] + [(phosphate (mg/dL)/3) × (0.309 × pH – 0.469)]; SIG (mEq/L) = SIDa – SIDe; FENa (%) = [(NaU(mEq/L) / Na^+ (mEq/L)) / (CrU (mg/dL) / creatinine (mg/dL))] x 100.

Statistical analysis

Quantitative data were tested for normality using the Kolmogorov-Smirnov goodness-of-fit model. Parametric data are shown as the means ± standard deviations and were analyzed using Student's t-test for non-paired variables. Non-parametric variables are presented as the medians with the 25th and 75th percentiles and were analyzed using the Mann-Whitney rank sum test. A modified Bonferroni correction for multiple comparisons was used to compare variables between survivors and non-survivors during the 4 days of the study, and the P value used for significance in the day-by-day comparisons was 0.0125. Friedman's test was used to analyze the data within the survivor and non-survivor groups during the 4 days analyzed. These data sets were also compared using a Bonferroni correction, resulting in a significance level for Friedman's test of 0.0125. *Post-hoc* analyses were performed with Dunnett's test using a significance level of 0.05. The graphs of non-parametric data are presented with box-and-whisker plots (the whiskers represent the 10th and 90th percentiles). Qualitative data are shown as occurrences and percentages and were analyzed with the chi-squared or Fisher exact tests, as appropriate. Spearman's rank correlation test was used to determine correlations between non-parametric variables. The SPSS 18.0 commercial Statistical Package for the Social Science (Chicago, IL) was used for the analyses.

RESULTS

From 235 patients admitted to our ICU from October 2009 to November 2010, 50 patients met the inclusion criteria and were included in the analysis (Figure 1). The main characteristics of the patients are shown in table 1. Eleven patients (22%) died in the ICU. ICU survivors and non-survivors did not differ in age, sex, diagnosis or SAPS 3 score at the time of admission to the ICU. Likewise, there was no difference between the two groups in the percentage of patients who needed mechanical ventilation, vasopressors or bicarbonate during the observation period. A higher percentage of non-survivors received diuretics during the observation period, and more non-survivors had renal replacement therapy after the observation period.

Traditional markers of renal function were compared between survivors and non-survivors during the observation period (Table 2). BUN was significantly greater in non-survivors during all days except day 1. Creatinine was significantly greater and

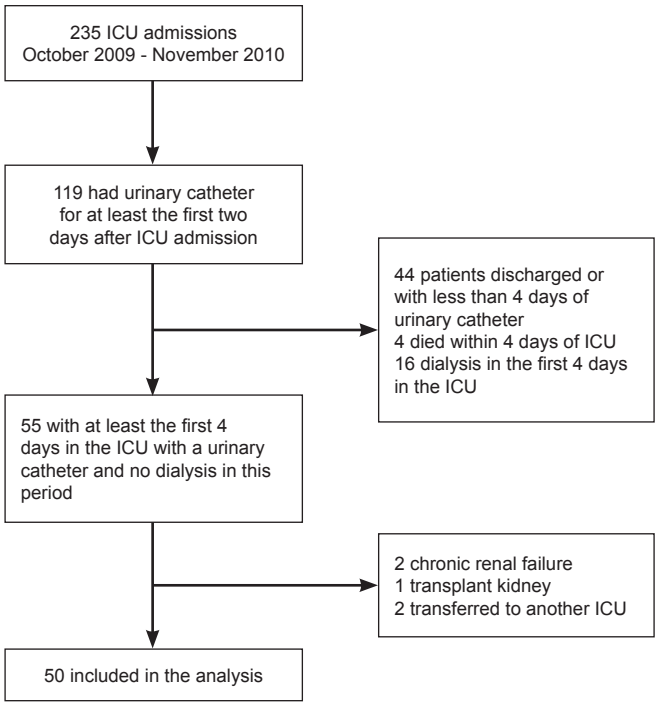

Figure 1 - Flow chart of patients included in the analysis. ICU - intensive care unit.

Table 1 - Patient characteristics and outcomes

	Whole group (N=50)	Survivors (N=39)	Non-survivors (N=11)	p value *
General characteristics				
Age - years	49±16	47±16	56±13	0.113
Male gender - N (%)	23 (46)	16 (41)	7 (64)	0.305
SAPS 3	47±15	47±16	46±14	0.788
First day total SOFA	6 (4-8)	7 (5-8)	6 (39)	0.754
Ideal body weight - kg	57±9	56±9	59±8	0.372
Comorbidities				
Heart failure - N (%)	5 (10)	3 (8)	2 (18)	0.301
COPD - N (%)	1 (2)	1 (3)	0 (0)	1.000
Cirrhosis - N (%)	2 (4)	2 (5)	0 (0)	1.000
Diagnosis at admission				0.821
Septic syndromes - N (%)	17 (34)	13 (33)	4 (37)	
Neurological syndromes - N (%)	18 (36)	14 (36)	4 (36)	
Stroke - N (%)	11 (22)	8 (21)	3 (27)	
Traumatic brain injury - N (%)	4 (8)	4 (10)	0 (0)	
Seizures - N (%)	3 (6)	2 (5)	1 (9)	
Respiratory failure - N (%)	8 (16)	7 (18)	1 (9)	
Postoperative - N (%)	5 (10)	4 (10)	1 (9)	
Other - N (%)	2 (4)	1 (3)	1 (9)	
ICU support				
Mechanical ventilation - N (%)	36 (72)	29 (74)	7 (64)	0.476
Vasopressors/ inotropics - N (%)	20 (40)	16 (41)	4 (36)	1.000
Diuretics - N (%)	24 (48)	15 (38)	9 (81)	0.028
Bicarbonate - N (%)	3 (6)	1 (3)	2 (18)	0.221
Renal replacement after the 4-day study period - N (%)	8 (16)	2 (5)	6 (54)	<0.001
Outcomes				
ICU LOS	10 (7-16)	10 (7-16)	7 (6-31)	0.916
Hospital death - N (%)	14 (28)	3 (8)	11 (100)	---------

SAPS - Simplified Acute Physiology Score; SOFA - Sequential Organ Failure Assessment Score; COPD - chronic obstructive pulmonary disease; ICU - intensive care unit; LOS - length of stay. Septic syndromes denote severe sepsis and septic shock. * p value of the comparison between survivors and non-survivors.

2-h creatinine clearance was significantly lower in non-survivors only at day 4. During the entire observation period, 24-h urine output, 24-h mean urinary flow, fluid intake and fluid balance were similar between groups. A significantly higher proportion of patients developed AKI in the non-survivor group (7 out of 11 patients in the non-survivor group (64%) compared to 7 out of 39 patients in the survivor group (18%) ($p < 0.01$)).

ClU and NaU on day 1 were significantly lower in patients who developed AKI during the observation period, both in survivors and non-survivors (Figure 2A). Although the median ClU and NaU were lower in non-survivors in comparison to survivors on day 1 (Figures 2B and 2C), this was restricted to patients who developed AKI during the 4 days of observation (Figure 2A). In the majority of the patients who developed AKI during the 4 days of observation, FENa was lower than 1% in both survivors and non-survivors (Figure 3). SIDu on day 1 was higher in patients who developed AKI during the 4 days of observation in both survivors and non-survivors (Figure 4).

Figure 5 compares SIDu and SIDa patterns. In survivors, SIDu was similar to SIDa at day 1 and significantly decreased by day 2. In non-survivors, SIDu stayed above SIDa during the entire observation period. ClU and NaU tended to be higher in survivors than in non-survivors on all days (Figures 2B and 2C). By contrast, KU tended to be greater in non-survivors (Figure 2D). In survivors, NaU was significantly greater on days 3 and 4 than on day 1. Twenty-four-hour mean urinary flow was positively correlated with ClU and NaU ($r=0.330$, $p < 0.001$ and $r=0.344$, $p < 0.001$, respectively), and creatinine was negatively correlated with ClU and NaU ($r= -0.517$, $p < 0.001$ and $r= -0.438$, $p < 0.001$, respectively). A significant negative correlation was found between KU and 24-h mean urinary flow

Table 2 - Renal characteristics of patients, categorized according to intensive care unit survival

		Day 1	Day 2	Day 3	Day 4	p value *
Blood urea nitrogen (mg/dL)	Survivors	20 (11-30)	24 (10-32)	17 (9-32)	19 (10-34)	0.910
	Non-survivors	35 (24-50)	43 (20-52) **	42 (18-59) **	40 (17-57) **	0.968
Creatinine (mg/dL)	Survivors	0.73 (0.57-1.11)	0.73 (0.58-1.01)	0.68 (0.52-1.04)	0.61 (0.50-1.09)	0.592
	Non-survivors	1.10 (0.76-1.43)	0.98 (0.76-1.46)	0.90 (0.68-1.79)	0.91 (0.76-1.87) **	0.964
Fluid intake (mL)	Survivors	2074 (1501-2901)	1805 (1314-3042)	1906 (1566-2619)	2044 (1422-2670)	0.779
	Non-survivors	2073 (1495-3242)	1969 (1396-2802)	1468 (571-1984)	1907 (709-2518)	0.609
24-h urine output (mL)	Survivors	1370 (910-2200)	1565 (1120-2742)	1730 (1035-2565)	1755 (875-3360)	0.546
	Non-survivors	1100 (730-2440)	1100 (600-2090)	1140 (900-2820)	1620 (585-2480)	0.992
24-h mean urinary flow (mL/kg/h)	Survivors	1.0 (0.6-1.6)	1.1 (0.8-2.0)	1.3 (0.8-1.9)	0.9 (0.5-2.7)	0.610
	Non-survivors	0.9 (0.5-1.6)	0.7 (0.4-1.3)	0.8 (0.6-1.8)	1.0 (0.4-1.7)	0.994
Fluid balance (mL)	Survivors	604 (-136-1313)	295 (-516-982)	350 (-796-947)	424 (-533-1060)	0.386
	Non-survivors	935 (128-1343)	592 (-586-1373)	-562 (-1149-590)	47 (-388-831)	0.233
2-h creatinine clearance (mL/min)	Survivors	94 (46-177)	113 (57-218)	77 (39-154)	118 (72-157)	0.298
	Non-survivors	61 (28-110)	45 (18-98)	56 (33-100)	31 (23-43) **	0.321
Renal SOFA	Survivors	0 (0-2)	0 (0-1)	0 (0-1)	0 (0-1)	0.861
	Non-survivors	0 (0-1)	0 (0-2)	0 (0-2)	0 (0-2)	0.988

SOFA - Sequential Organ Failure Assessment Score. * Friedman's test over time.** p<0.0125 vs. survivor group, Mann-Whitney rank sum test with Bonferroni's correction for multiple comparisons.

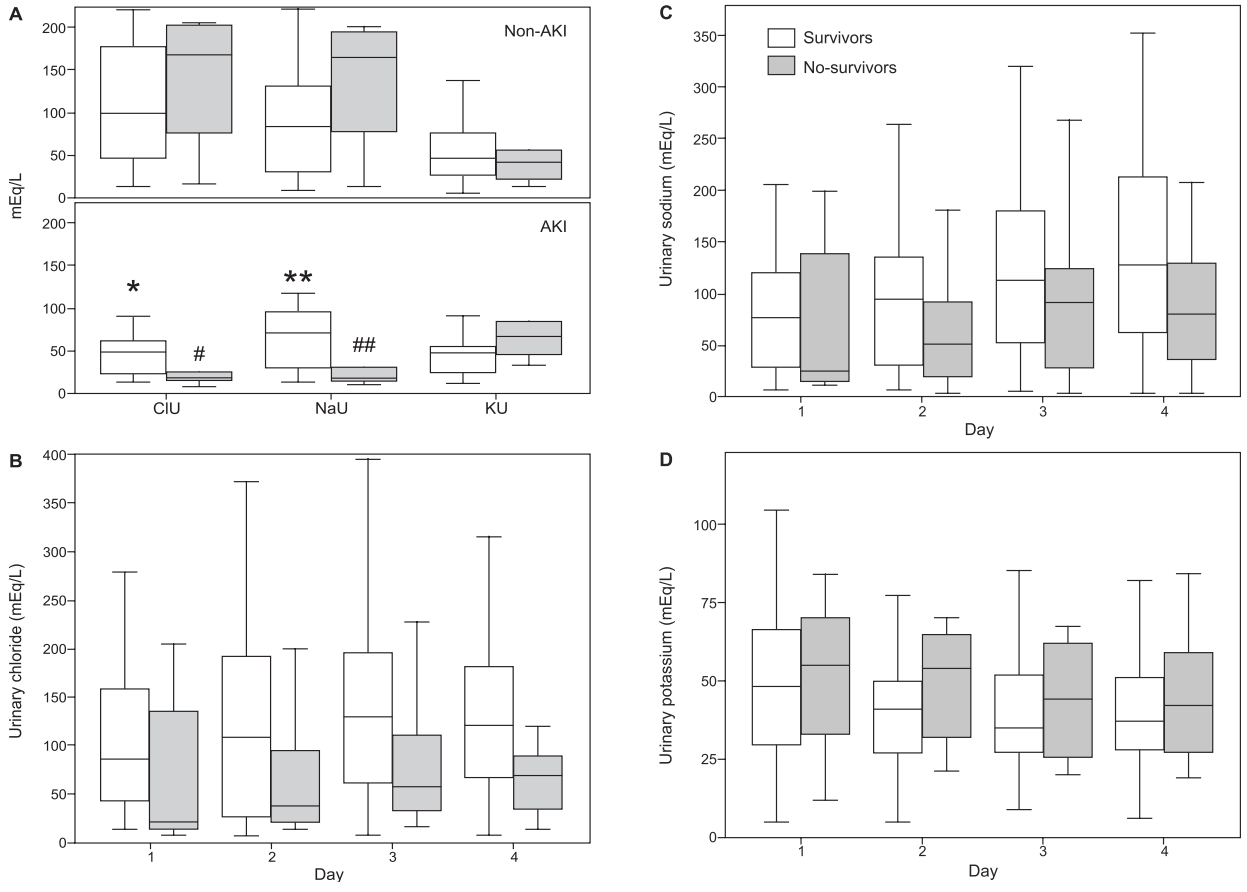

Figure 2 - A) Urinary electrolytes on day 1 in patients who did or did not develop acute kidney injury during the 4-day observation period in survivors and non-survivors. **B, C, D)** Urinary electrolytes during the 4-day observation period in survivors and non-survivors. AKI - acute kidney injury; ClU - urinary chloride; NaU - urinary sodium; KU - urinary potassium. Difference between survivors with AKI and without AKI: * ClU (p = 0.001); ** NaU (p = 0.01). Difference between non-survivors with AKI and without AKI: # ClU (p = 0.04); ##NaU (p = 0.05). Difference among the days: **B** - ClU (p = 0.260 for survivors and p = 0.607 for non-survivors); **C** - NaU (p = 0.011 for survivors and p = 0.844 for non-survivors). **D** - KU (p = 0.317 for survivors and p = 0.756 for non-survivors).

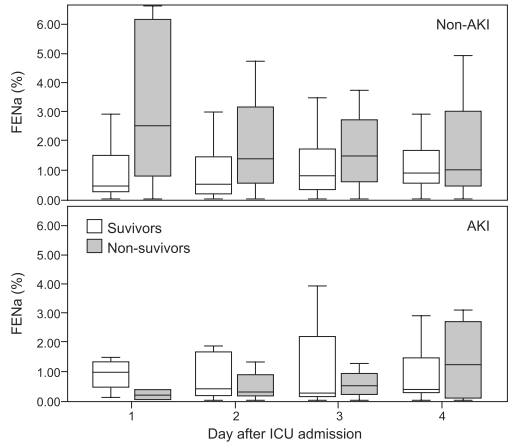

Figure 3 - Fractional excretion of sodium in patients who did or did not develop acute kidney injury during the 4-day observation period in both survivors and non-survivors. FENa - fractional excretion of sodium; AKI - acute kidney injury; ICU - intensive care unit.

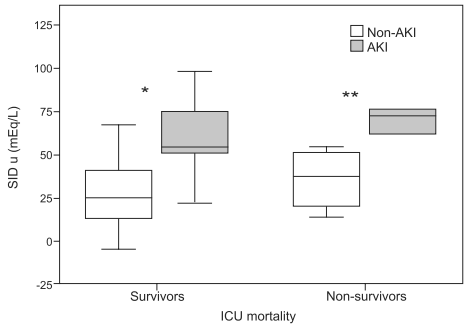

Figure 4 - Urinary strong ion difference on day 1 in patients who did or did not develop acute kidney injury during the 4-day observation period in both survivors and non-survivors. SIDu - urinary strong ion difference; AKI - acute kidney injury; ICU - intensive care unit. Difference between survivors with AKI and without AKI: * p = 0.002. Difference between non-survivors with AKI and without AKI: ** p = 0.05.

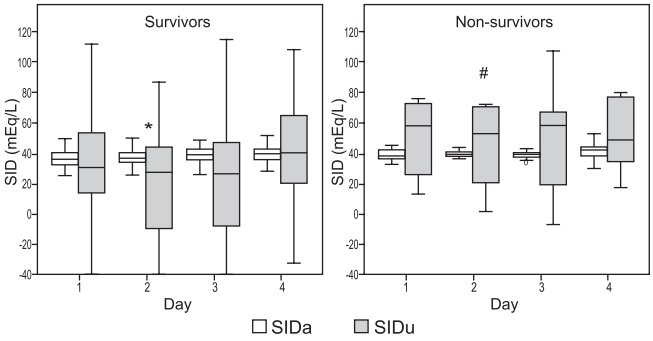

Figure 5 - Strong ion difference in plasma (SIDa) and urine (SIDu) during the 4 day observation period in both survivors and non-survivors. Difference among the days in survivors: SIDa (P = 0.184) and SIDu (P = 0.062). Difference among the days in non-survivors: SIDa (P = 0.584) and SIDu (P = 0.923). On day 2, the difference between SIDa and SIDu in survivors (* P < 0.0125). On day 2, the difference between SIDu of survivors and non-survivors (# P < 0.0125).

(r= -0.237, p < 0.01), but there was no correlation between KU and creatinine (r= 0.059, p=0.412).

In table 3, traditional and physicochemical blood acid-base variables are compared between ICU survivors and non-survivors during the first 4 ICU days. Over this time, survivors had a significant increase in pH and SBE, which was associated with non-significant increases in SIDa and SIDe and decreases in weak acids (albumin and phosphate). Neither lactate nor SIG was different between or within groups. Both Na^+ and Cl^-, the main determinants of SID, showed a progressively increasing trend in both groups. Phosphate was significantly greater in non-survivors compared to survivors on day 4.

Table 3 - Blood physicochemical characteristics of patients, categorized according to intensive care unit survival

		Day 1	Day 2	Day 3	Day 4	p value #
pH	Survivors	7.37 (7.32-7.42)	7.38 (7.34-7.41)	7.40 (7.37-7.43)**	7.42 (7.39-7.44)**	< 0.001
	Non-survivors	7.38 (7.35-7.45)	7.40 (7.37-7.48)	7.40 (7.39-7.42)	7.39 (7.36-7.42)	0.662
PCO_2 (mm Hg)	Survivors	37 (31-43)	40 (34-46)	39 (33-47)	38 (32-44)	0.702
	Non-survivors	39 (34-42)	39 (34-43)	40 (36-46)	40 (34-44)	0.949
SBE (mEq/L)	Survivors	-3.0 (-6.3-0.13)	-2.0 (-4.6-1.0)	-0.5 (-3.9-1.6)	-0.3 (-2.1-3.1)**	0.006
	Non-survivors	-2.4 (-4.1-3.5)	0.3 (3.2-4.8)	-0.1 (-2.5-1.9)	-1.4 (-3.6-2.5)	0.776
HCO_3^- (mEq /L)	Survivors	21 (18-25)	23 (20-26)	23 (20-26)	24 (21-27)	0.033
	Non-survivors	22 (21-27)	24 (22-28)	25 (22-27)	23 (21-27)	0.802
Lactate (mEq /L)	Survivors	1.9 (1.5-2.5)	2.0 (1.5-2.4)	1.8 (1.4-2.3)	1.6 (1.3-2.5)	0.476
	Non-survivors	2.4 (1.8-3.8)	2.3 (1.9-3.4)	2.8 (2.2-4.1)	1.9 (1.2-3.2)	0.067
SIDa (mEq /L)	Survivors	36 (33-41)	36 (34-40)	39 (35-42)	40 (36-43)	0.184
	Non-survivors	39 (37-44)	39 (38-43)	39 (37-41)	42 (38-46)	0.584
SIDe (mEq /L)	Survivors	29 (27-36)	32 (29-36)	33 (29-37)	34 (30-37)	0.218
	Non-survivors	33 (30 37)	35 (28-37)	35 (30-37)	35 (29-36)	0.999
SIG (mEq /L)	Survivors	5.2 (2.8-8.6)	4.3 (2.9-6.9)	5.1 (3.0-7.9)	4.5 (3.3-6.5)	0.886
	Non-survivors	4.5 (1.5-10.0)	5.7 (2.6-7.7)	4.5 (3.8-9.0)	7.7 (3.5-13.5)	0.489
Albumin $^-$ (mEq /L)	Survivors	8.1 (7.0-8.9)	7.6 (6.7-8.5)	7.3 (6.9-8.4)	7.6 (7.1-8.6)	0.026
	Non-survivors	6.9 (5.7-9.4)	7.0 (5.8-9.6)	7.8 (5.3-9.2)	7.0 (5.5-8.2)	0.859
PO_4^{-2} (mEq /L)	Survivors	1.9 (1.3-2.4)	1.3 (1.2 1.7)**	1.2 (1.0-1.7)**	1.5 (1.3-1.9)	0.001
	Non-survivors	2.0 (1.6-3.2)	1.5 (1.1-2.8)	1.7 (1.1-2.5)	2.3 (1.4-2.6)***	0.338

PCO_2 - partial pressure of carbon dioxide; SBE - standard base excess; HCO_3 - bicarbonate; SIDa - apparent strong ion difference; SIDe - effective strong ion difference; SIG - strong ion gap; PO_4^{-2} - phosphate.* Friedman's test over time. ** p< 0.05 vs. day 1, Dunnett's post-hoc analysis. *** p < 0.0125 vs. survivor group, Mann-Whitney rank sum test with Bonferroni's correction for multiple comparisons.

DISCUSSION

In this preliminary study, we described the urinary biochemistry profile of a small group of critically ill patients in parallel to other parameters frequently used for acid-base and renal function evaluation. In our cohort, the incidence of AKI using the AKIN creatinine criterion was significantly higher in non-survivors during the observation period (64% vs. 18% in survivors). This difference became evident on day 4 (Table 2) and was associated with a higher percentage of non-survivors requiring renal replacement therapy after 4 days of observation (Table 1). Figures 2 and 4 suggest that low levels of NaU and ClU and a high (above-normal) level of SIDu on day 1 were frequently present in patients who had AKI in the first 4 days in the ICU. Although the median renal SOFA was 0 in both groups during the 4-day observation period, the low levels of ClU and NaU (Figures 2B and 2C), high levels of KU (Figure 2D) and SIDu (Figure 5), and the increased BUN, increased phosphate and lower creatinine clearance demonstrate that the majority of non-survivors had some degree of renal dysfunction from the start of the study, even in the face of normal creatinine. A recent study by Beier et al.[16] also demonstrated that higher BUN may be a strong predictor of mortality in critically ill patients, independent of normal creatinine.

One of the classic clinical uses of urinary biochemistry is to differentiate a reversible renal dysfunction ("pre-renal") from acute tubular necrosis (ATN). The potential use of urinary electrolytes as a parameter to guide fluid resuscitation to reverse AKI has been recently reviewed.[17] Although we did not intend to determine reversibility by evaluating urinary electrolytes, the urinary electrolyte data of our study could reflect decreased glomerular perfusion pressure, the main mechanism associated with decreased urinary sodium and chloride excretion. In our patients with evidence of a decreased glomerular filtration rate, the low NaU and ClU also suggest a preserved tubular capacity to reabsorb sodium and chloride. Despite the use of diuretics in our cohort, we found a low FENa (<1%) (Figure 3) and a low fractional excretion of urea (FEUr <35%) (data not shown) in patients with AKI, among both survivors and in non-survivors. The lower NaU and higher KU in non-survivors (Figure 2) may have been due, in part, to an enhanced exchange of Na^+ and K^+ in the distal tubule, indicating an adequate tubular response and exacerbated activation of the renin-aldosterone system.

Our results are in agreement with previous experimental data, which also suggest that a loss of glomerular filtration pressure explains, in large part, the urinary biochemistry findings in AKI, even with increased total renal blood flow, as occurs in hyperdynamic sepsis.[18] A recent review also focused on glomerular hemodynamics as having a central role in the pathogenesis of AKI,[19] which is consistent with the supposition that kidney injuries in critically ill patients, especially septic patients, are more functional than structural.[20] Therefore, NaU and ClU seem to monitor glomerular function, and SIDu may be viewed as an indicator of tubular acidifying capacity, signaling an early urinary acidification dysfunction in AKI.

SIDu as a surrogate of kidney function, in the presence of metabolic acidosis, has recently been evaluated.[9,11] Masevicius et al.[11] reported that most of the critically ill patients with metabolic acidosis showed inappropriate renal compensation because a minority of them presented a negative SIDu. However, we believe that decreases in SIDu below the level of plasma SID (i.e., still positive values of SIDu), as occurred in most of the survivors in our study (Figure 5), is an appropriate renal response because the majority of survivors did not meet the AKIN creatinine criteria for AKI. In agreement with their results, we found negative SIDu to be quite rare in non-survivors (Figures 4 and 5), a finding that is most likely related to the high prevalence of AKI in this group. We did not separate the patients with and without pure metabolic acidosis, which could also explain, at least in part, the differences between our results and theirs. Moviat et al.[9] also proposed that impaired renal function is associated with a higher SIDu in patients with metabolic acidosis. Their findings were limited by a single measurement of a simplified SIDu (NaU - ClU) per patient and a simple definition of impaired renal function, as they used an isolated creatinine measurement. Our study reinforces the notion that simple urinary biochemistry can be used from the first day of ICU admission to help monitor kidney function and has a potential role in predicting AKI development.

Although diuretic use directly affects urinary electrolyte composition, increasing spot NaU in both transient and persistent AKI,[21] we did not exclude patients who used diuretics during the observation period. The main reason for this was that diuretics are frequently used in the management of critically ill patients. A greater proportion of patients used diuretics in the non-survivor group, a finding that must be interpreted carefully. First, no causal relationship could be identified between diuretic use and increased mortality. Our opinion is that diuretics could partially explain the similar urine output between survivors and non-survivors. Regarding the interpretation of urinary

electrolytes, we believe that, given the similar urine output between the two groups, the low levels of NaU and ClU in non-survivors may be viewed as an impairment to natriuresis and chloriuresis, which was not adequately solved even with greater diuretic administration. Loop diuretics increase urinary acidification by enhancing NH_4^+ and Cl^- excretion in relation to Na^+ and K^+.[22] Hence, higher SIDu and lower NaU and ClU, as found in non-survivors, could not be attributed to more frequent use of diuretics, whereas these findings are compatible with a greater prevalence of AKI in non-survivors.

As previously shown,[12,23] ICU survivors had a progressive improvement in pH, mostly due to the correction of metabolic acidosis. This improvement, with daily increases in SBE, reflected a combination of small increases in plasma SID and decreases in weak acids (albumin and phosphate) (Table 3). Decreases in SIDu (Figure 5) correspond to the kidney's contribution to metabolic acidosis correction. Low SIDu values reflect the kidney's ability to excrete NH_4^+, the main mechanism for increasing acid excretion after an acid load.[24] Thus, in kidneys with preserved function, a lower SIDu implies an increased excretion of NH_4^+.

Taking into account all data regarding urine biochemistry, it seems that major differences between survivors and non-survivors were associated with an increased AKI prevalence in the latter group. Hence, AKI can be viewed as an inability to address acid-base metabolic disturbances, which may be detected before major increases in creatinine or decreases in urine output.

The higher SIDu observed in non-survivors could also be explained by increased levels of unmeasured anions in their urine, even with appropriate urinary NH_4^+ levels. However, this hypothesis is weakened because serum unmeasured anion concentrations, as assessed by SIG, were similar between survivors and non-survivors (Table 3). The diagnosis of renal tubular acidosis (RTA) is difficult to exclude using the data available from our study. Although RTA is classified into distinct types, they are all characterized by hyperchloremic acidosis and high urinary SID.[10] Many chemicals, including antibiotics frequently used in the ICU, may contribute to some type of RTA. Considering that glomerular filtration is usually not impaired in RTA, it was unlikely to be a major cause of the high SIDu in non-survivors.

There are some weaknesses of our study that deserve mention. First, the small sample size likely prevented some real differences from becoming evident, especially because urine electrolytes have a large range of physiological concentrations. Diuretic use is also a confounding factor that we could not adjust for; however, as discussed above, in the absence of diuretics, the differences would most likely have been even greater between survivors and non-survivors. In addition, our work did not intend to explore a more detailed explanation for the persistently high SIDu in non-survivors, which would require parallel measurements of urine pH, direct urinary NH_4^+ measurement, and other investigations. Unfortunately, we did not obtain data from the period before ICU admission to compare the amounts of fluid received by survivors and non-survivors. We do not think that the differences in urine biochemistry were due to higher amounts of sodium and chloride received during resuscitation in survivors prior to ICU admission. Our results cannot exclude this possibility, however. During their ICU stay, fluid intake and fluid balance were similar between the two groups.

It is important to emphasize that our results were obtained in a selected population of critically ill patients. Very sick patients who died or needed renal replacement therapy before day 4 of their ICU stay, patients with a low risk of death or AKI that were discharged early from the ICU and patients who were managed without a urinary catheter are not represented in our study (Figure 1). This may be interpreted as a selection bias and may explain the similarity in many variables between survivors and non-survivors, such as SAPS 3, vasopressor use and mechanical ventilation. However, this similarity helps to demonstrate that in our sample, urinary biochemistry monitoring was useful in distinguishing patients who otherwise would be considered to have similar renal function and prognosis based solely on classical variables such as urine output, serum creatinine (Table 2), and severity scores (SAPS 3 and SOFA) (Table 1).

CONCLUSION

The study does not have sufficient power to allow any definitive conclusion regarding the roles of SIDu and urinary electrolytes in monitoring critically ill patients. Additionally, the small sample size precluded a more thorough evaluation of the accuracy of AKI diagnosis. However, this preliminary study is the first to suggest that daily urinary electrolyte monitoring may be a potentially useful tool in AKI monitoring, in combination with other simple and easily measurable parameters. Due to the limitations cited above, this article should prompt larger studies that will effectively evaluate the hypotheses generated by these initial findings. In fact, a more extensive prospective, observational study is already underway

in our ICU to evaluate the potential utility of urinary biochemistry in AKI monitoring. This topic is of major interest to intensivists and nephrologists.

Contributions of the authors

AT Maciel conceived the study and research proposal, developed the study design, collected the data and wrote the initial manuscript. M Park collected and analyzed the data. E Macedo conceived the study and proposal, performed the data analysis and wrote the manuscript. All authors agreed to the final version of the manuscript and agreed to submit it for publication.

RESUMO

Objetivo: Sobreviventes e não sobreviventes da unidade de terapia intensiva apresentam perfis ácido-básicos distintos. A regulação renal de eletrólitos urinários e a diferença de íons fortes urinários têm papéis principais na homeostase ácido-básica. O objetivo deste estudo foi avaliar a potencial utilidade da mensuração diária dos eletrólitos urinários na monitorização ácido-básica e da função renal.

Métodos: Foram registrados, prospectivamente e diariamente, parâmetros ácido-básicos plasmáticos e marcadores tradicionais da função renal, em paralelo à medição dos eletrólitos urinários em pacientes com sonda vesical internados na unidade de terapia intensiva. Os pacientes que permaneceram na unidade de terapia intensiva com sonda vesical por pelo menos 4 dias foram incluídos neste estudo.

Resultados: Dos 50 pacientes incluídos neste estudo, 22% vieram a óbito durante a internação na unidade de terapia intensiva. A incidência de lesão renal aguda foi significativamente maior nos não sobreviventes, durante os 4 dias de observação (64% *versus* 18% em sobreviventes). O cloreto e o sódio urinário foram mais baixos, e a diferença de íons fortes urinários mais alta, no 1º dia, em pacientes que desenvolveram lesão renal aguda tanto nos sobreviventes como nos não sobreviventes. Ambos os grupos tiveram débito urinário semelhante, embora os não sobreviventes tenham apresentado diferença de íons fortes urinários persistentemente mais alta durante o período de observação. Os sobreviventes apresentaram melhoria progressiva no perfil metabólico ácido-básico devido ao aumento, no plasma, da diferença de íons fortes e à diminuição dos ácidos fracos. Essas mudanças foram concomitantes à diminuição da diferença de íons fortes urinários. Com relação aos não sobreviventes, os parâmetros ácido-básicos não tiveram alteração significativa durante o seguimento.

Conclusão: A avaliação diária dos eletrólitos urinários e da diferença de íons fortes urinários é útil para a monitorização ácido-básica e da função renal em pacientes críticos, tendo perfis distintos entre sobreviventes e não sobreviventes na unidade de terapia intensiva.

Descritores: Cuidados críticos; Acidose; Desequilíbrio hidroeletrolítico; Lesão renal aguda; Monitorização fisiológica; Prognóstico

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